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# INSTRUCTIONAL TECHNIQUE IN HETEROCYCLIC CHEMISTRY

## COMPUTER ANIMATION: A NEW METHOD FOR TEACHING, COMMUNICATION, AND REPRESENTATION OF KNOWLEDGE ABOUT REACTIONS IN HETEROCYCLIC CHEMISTRY

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*We propose the use of computer animation techniques for representation of knowledge about organic reactions, in particular as applied to syntheses and transformations of heterocycles. We discuss general questions of the methodology of "chemical animation" as a new method of communication via electronic journals and an effective teaching method. We illustrate the technical and methodological means allowing us to solve the resulting problems, using as an example the operation of a specific program.*

Chemists not only investigate compounds or reactions; they attempt to collect as much already known information as possible and to communicate new results obtained to the scientific community in the best way possible. It is specifically this aspect of the routine work of a scientist, in our opinion, which has been rapidly changed by computers. The printing press has been displaced by the text editor. The ruler and template have been replaced by a powerful editor for drawing and manipulation of chemical structures. Electronic databases of properties, spectra, and reactions have become an alternative to paper card catalogs and awkward handbooks. Journals (or at least a listing of materials published in them) are published simultaneously in printed and electronic versions. An undeniable advantage of the latter is the speed of publication and the limitless possibilities for computer graphics. Along with conventional conferences, computer teleconferences have appeared. Electronic mail is transmitted faster than conventional mail. Editorial staff of journals and financing organizations increasingly often require a computer copy of the printed text. The decrease in the cost and the increase in the speed and power of computers are making these trends irreversible. It is a disadvantage to not have a computer, but it is even more of a disadvantage to have a computer and not use all its capabilities to the fullest.

In order to avoid lagging catastrophically behind, the chemist is forced to master the profession of "computer user"; and the university chemist, in order to prepare a fully-equipped generation of future scientists, must teach the students the ABC's of computer literacy as early as possible. The first route to computer education and self-education is passive adaptation to already existing and newly proposed types of "hardware and software." A second route, independent design of programs, has increasingly become the province of highly professional programmers joining together in high-power collectives. Nevertheless, there is a third, intermediate route: creative use of application packages for development of new software (for example, demonstration software). In this case, the user of the ready-made program (such as a compositor, designer, or scientist) acts simultaneously as an active creator of a product having independent value.

Over the course of a number of years, our research group has developed the program kit Heterocycland, intended for design of heterocyclic structures and reactions [1-3], in particular for prediction of new recyclizations or new strategies for synthesis of azines. One of the program modules includes the use of computer animation techniques for a graphic and dynamic demonstration of rather complicated synthesis routes or heterocyclic transformations. A set of such animated film clips was effectively used by the author over the course of five years in teaching a course on heterocyclic chemistry in the chemistry department of Moscow State University. The goal of this report is to provide a brief analysis of the problems connected with application of animation techniques in organic chemistry, considering our experience accumulated in this field.

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A model of a chemical structure represented on a sheet of paper or on a photograph remains two-dimensional. Using the shadowgraph technique, optical illusions (the stereoscopic pair principle, a hologram) or agreeing on methods of projection onto the plane (the IUPAC rules), we can come close to the real three-dimensionality of the molecules. On a flat computer display, the image of the molecular model as before remains flat. Nevertheless, a more adequate illusion of three-dimensionality for the model is created by means of a rapid alternation of a sequence of two-dimensional images on the screen, for example as a result of the apparent possibility of rotation of the object in space. In fact, the computer allows us to compensate for the missing third geometric coordinate using the time coordinate.

A chemical reaction is a change in the coordinates of the atoms and electrons (to a rough approximation, the bonds) in space and time. We can consider a reaction to be a continuous change of the molecules in the four-dimensional space–time continuum. However, chemists are forced to replace the continuity by discreteness (the left-hand and right-hand side of the equation and the intermediates) and the four-dimensionality by a two-dimensional flat sheet. Clearly in this case the image of the chemical reaction on the computer display has more advantages, both with respect to the number of apparent changes of the chemical structure and with respect to the possibility of creating an illusion of temporal continuity by means of discrete images.

Let us emphasize that the problem of computer animation in chemistry is at the beginning of its journey, and only the first tentative steps have been taken in this field (see, for example, the report in [4]). The precursor of computer animation in natural science is the genre of popular-science cinematography and animation, which has practically vanished from university auditoriums. A major factor still holding back the use of computer animation is financial. Not every university is able to acquire a package of serious animation programs, which are generally oriented toward creation of commercial advertising.

It is appropriate to isolate the following cases when the use of computer animation techniques for dynamic representation of chemical reactions may have the greatest advantages over static models:

1) visualization of the movement of reagents over a multidimensional potential energy surface;

2) change in the overlap of each orbital (in particular, the frontier orbitals over the course of the reactions;

2) change in the electron density characteristics (for example, the appearance of and change in the types of critical points of the Laplacian of the electron density) of the reagents over the course of the reaction;

4) change in the shape and topology upon reaction of molecules represented using two-dimensional objects (conventional Stewart–Briegleb models, the surfaces of the molecules taking into account van der Waals radii of the atoms, etc.);

5) redistribution of bonds in classical structural formulas of the molecules (for example, Lewis diagrams) or in molecular graphs.

We note that the first three cases require quite serious calculations for construction of each elementary frame of the dynamic picture of the reaction; and the fourth case, as a minimum, requires specific software for describing the changes in the surfaces. The simplest method for imparting dynamic features to the static picture of the reaction proves to be the last case, the closest to the conventional representations of organic chemists. However, we do not know of any examples of the use of animation programs as applied to conventional structural formulas.

It is specifically this case of dynamic modeling of reactions that we consider below. For the computer animation, we used the simple and well known program Fanta Vision, designed for DOS users. Let us briefly consider the capabilities of this program. In the drawing mode, the user has three alternatives for choosing the dimensionality of the object to be imaged:

1) the object as a set of 0-dimensional elements (points),

2) a set of 0- and 1-dimensional elements (for example, a closed or open broken line,

3) a set of 0-, 1-, and 2-dimensional elements (for example, colored polygons, convex and nonconvex.

For convenience, we specify circle or rectangle templates and the capability of changing the dimensionality of the component elements for any represented object (for example, a continuous rectangle or circle can be instantaneously replaced by a set of points and lines or only points). The object can be subjected to various topological distortions or geometric changes: translating, changing the size, turning in different planes, reflecting relative to some line, distorting relative to the center of gravity, etc. The operations can be combined.

An ensemble of objects (no more than 16) forms a frame, and the number of frames is practically unlimited. In order to simulate dynamics, it is sufficient to copy the required object to the next frame, where the required alterations are performed on it. The computer stores the correspondence between the object and the preceding and the next frames, and breaks down the procedure for the change into a rather large number of steps. Thus the need to create intermediate frames is

eliminated: they appear automatically. The time each frame is shown and the speed of the changes can be regulated. This allows us to achieve a full illusion of continuity, or to go from smooth transformations to jumpwise transformations.

Text can also be an object (letters in the program are objects made from 0- and 1-dimensional elements). In addition, the user has available a complete library of sound effects (more than 40) and a variable color scale (16 colors). The demonstration capabilities resemble the capabilities of the videotape recorder: stop-frame, running faster or slower, running backward, turning off the sound, skipping the current animated film clip and going on to the next.

Obviously, the simplest type of structural models for molecules (the molecular graph) is naturally represented by an object consisting of 0- and 1-dimensional elements. Multiple bonds and labels for heteroatoms are easily placed as additional one-dimensional elements. The proposed arsenal of imaging techniques thus prove to be quite sufficient for representing rather complex structural formulas of molecules onscreen, such as reagents entering into chemical reaction.

It is not especially difficult to show in a continuous fashion the approach or collision of molecules, vibrations of individual bonds, or rotation of some moieties relative to others. However, we have encountered the interesting problem of representing the discrete stages of bond breaking and formation in a continuous fashion. We note that within the framework of graph theory, this problem is insoluble: in a molecular graph, the bond either exists or it does not exist, and it cannot appear or disappear in a continuous fashion. With the goal of approaching as closely as possible a continuous display of the image of the reaction and preserving the methodological correctness from the standpoint of the chemistry, we used the following algorithm. As was already said above, the program allows us to transform objects of different dimensionality into each other. In the simplest case, a segment can be transformed into a pair of points. Since a pair of points is the standard representation for an unshared pair in chemistry, in describing heterolytic breaking/formation of a single bond we required the simultaneous appearance/disappearance of an electron pair on the corresponding atom. This is equivalent to the simple and natural rule of conservation of the number of electron pairs. Analogously, in describing delocalization over a conjugated chain, smooth and continuous redistribution of double bonds was accompanied by charge compensation, with indication of the location of the electron pair.

The assumed restrictions allowed us to quite correctly and "almost continuously" describe, in the form of short animated film clips, the transitions between the starting molecules and the products considering generally accepted intermediates (for example, in reactions of electrophilic or nucleophilic addition and substitution). It seemed methodologically useful to us to describe the following sample aspects of heterocyclic chemistry using animation techniques:

1) classical name rearrangements and recyclizations of heterocycles (the Dimroth, Yur'ev, Kost–Sagitullin, Cornforth, Boulton–Katritzky, Zinke–König, Hafner reactions), including cases of degenerate rearrangements;

2) individual examples of multicomponent cyclizations and multistep recyclizations with a complex design (for example, the Hantsch synthesis of pyridines or the synthesis of indoles from pyridinium salts);

3) individual fundamental aspects of heterocyclic chemistry, in particular the difference between $\pi$-rich and $\pi$-deficient heterocycles, the problem of $\alpha,\beta$-selectivity in the series of heterocycles with a pyrrole type heteroatom, the Fischer reaction, desulfurization of thiophenes.

Conservation of orbital symmetry in the Diels–Alder reaction is separately represented. Demonstrations are accompanied by special sound effects (in a number of cases, entertaining embellishment) and topics intended to enliven and stimulate the learning process. Teaching experience has shown that demonstrations of reactions in which a problematic situation arises are especially effective (such as when the reaction mechanism at first glance is not obvious or has alternatives). Thus for quasidegenerate reactions (the Dimroth rearrangement with an apparent *endo-exo* migration of the substituent), the final design of the reaction is initially demonstrated and only then is the multistep ANRORC mechanism worked out.

We should note that the demonstration variations provided by the program increase the methodological value of the dynamic description of the reactions. Thus the "stop-frame" method allows us to stop the view at any moment in the stage of any interesting intermediates. This is especially important for representation of the symmetry of the intermediates of degenerate and quasidegenerate rearrangements, where the symmetry does not clearly follow from the structures of the starting compounds and end products. The ability to run the sequence backward in each stage is a unique illustration of the principle of microscopic reversibility.

Creation of animated film clips for a complex multistep reaction requires knowing the correct selection of the most significant intermediates. This problem is most acute for chains and rings with several heteroatoms, since there are alternative choices for the significant tautomers. The limited number (at most 16) of objects in a frame should be considered a purely technical problem. Thus, in order to represent pyridine, we require five objects (a hexagon, three double bonds, a symbol for

the atom and an electron pair). However, we can avoid the problem by using the "trick" of repeatedly traversing the same bonds in imaging the polygon. The second possibility involves the fact that a fragment of the molecule retained during the course of the reaction is declared part of the background and then is not considered as an object. The indicated technical details allow us to easily present in dynamic form information about multistep transformations of very complicated molecular skeletons containing several tens of atoms. Thus the familiar program becomes a powerful new tool for a new (dynamic) method for representation of knowledge about reactions of classical structures.

So, let us sum up briefly. Application of computer animation allows

— *the researcher*: to more thoroughly sort out the details of the mechanism of the reaction under study (the structure of possible intermediates, the sequence of elementary steps, etc.), to compactly describe the result of complex transformations (combining statics and dynamics, looking at the integral whole and the details), and finally, in clear form to represent the results achieved to the scientific community via modern electronic journals;

— *the teacher*: to present very complicated aspects of heterocyclic chemistry in accessible and popular form, replacing chalk and blackboard (overhead and projector) with the computer display;

— *the students*: to better grasp the material presented by the teacher, and in carrying out independent assignments (creating their own animated film clips on a specified theme) to more thoroughly master the subject and to improve their computer skills.

The software created is accessible, can be used on IBM PC computers, and is distributed at no charge over the computer networks. E-mail for orders: bev@sci.chem.msu.su.

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